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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO. <i>KM</i>
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED: *9*

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/407,605

Applicant(s)

MILLER ET AL.

Examiner

Hope A. Robinson

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- 1) ☒ Responsive to communication(s) filed on 23 January 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 64-135 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 64-135 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
 2. ☐ received in Application No. (Series Code / Serial Number) _____.
 3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Information Disclosure Statement (S.) (PTO-1449) Paper No(s): 5,6

- 15) ☐ Notice of Informal Patent Application (PTO-117)
- 19) ☐ Other

Art Unit: 1653

DETAILED ACTION

1. Applicant's election without traverse of Group I (claims 1-48 and 58-63) in Paper No. 7 is acknowledged. It is noted that applicant has canceled all the originally filed claims and submitted new claims 64-135 directed to the invention of Group I.

Oath/Declaration

2. Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 64-135 are rejected under 35 U.S.C. 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

Art Unit: 1653

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that the invention relates a synthetic nucleic acid sequence which encodes a protein or a portion thereof, wherein at least one non-common codon or less-common codon has been replaced by a common codon, and wherein the synthetic nucleic acid sequence includes a continuous stretch of at least 90 codons all of which are common codons. The claims also recite a "continuous stretch of 90 codons with no particular sequence associated with the claims (see also where the claims recite at least 80 base pairs). In addition, there is no indicia of what "portion thereof" of the protein is encoded by the synthetic nucleic acid. Further the specification asserts that in a preferred embodiment the nucleic acid sequence encoding a protein has at least 30, 50, 60, 75, 100, 200 or more non-common or less-common codons replaced with a common codon. The specification further asserts that in a preferred embodiment, the number of non-common or less-common codons replaced is less than 15, 14, 13, 12, 11, 10, 9, 8, 6, 5, 4, 3, 2, or 1 (see page 3, the same is said for the number of non-common or less-common codons remaining). Note that less than 1 can mean 1/2, 0, -1 etc. How can less than 1 codon that is non-common or less-common be replaced or remain if given the above numbers? In addition it is recited in the claims and disclosed in the specification that at least one non-common or less-common codon is replaced, therefore, how can at least 1 be interpreted as less than 1, the

Art Unit: 1653

includes 30, 50, 60, 75 or 100. Furthermore, if all these different conditions of at least 1, at least 30, 50... and less than 15, 14, 13... are all preferred embodiments as disclosed on page 3, how would one of skill in the art know what condition to use to practice the claimed invention as they are not equivalent. Therefore, the invention is not adequately described as the specification does not provide sufficient guidance commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 64-135 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64 and the dependent claims hereto are indefinite because the claim recites the replacement of less-common and non-common codons in a sequence that encodes a protein without indicating if the same protein will be encoded by the replacement codon (see also claims 69, 73, 81, 85, 89, 97, 100, 103, 113, 116, 119, 120, 125, 130 and 135). Also the claim does not require to a specific sequence in reciting "at least 90 codons"(see also claims 69, 73, 81, 85, 89, 97, 100, 103, 113, 114, 116, 119, 120, 125, 130 and 135).

Art Unit: 1653

Claim 67 is indefinite because the claim recites "less than 15" and less than 15 means 14, 13, 10.6, 10.5, 1, 1/2, 0 or -1, etc. It is unclear for example how we can get a replacement of -1 codon or 0 (see also claims 72, 75, 83, 87, 91, 99, 101 and 105).

Claim 73 is indefinite because the claim recites "amino acids" instead of "amino acid residues" (see also claims 78, 89, 103 and 113). The claim is also indefinite for the recitation of "at least about 90 amino acids", note that "at least" is a narrow range and "about" is a broader range which goes outside the "at least" range (see also claim 85 where "comprise at least" is recited and "comprise" goes out side of "at least").

Claim 82 is indefinite because the claim recites the acronym "BDD" without the spelled out word meaning. In addition, the claim is indefinite for reciting "the factor VIII protein has one or more of the following characteristics: (c) it is inserted into a non-transformed cell". It is "presumed" that applicant meant to indicate that the factor VIII polynucleotide is inserted into a non-transformed cell and not the actual factor VIII (see also claims 86, 90 and 102).

Claim 119 is indefinite because the claim is directed to "a method for preparing a synthetic nucleic acid sequence" the method does not have this product as an endpoint.

Claims 120, 125, 130 and 135 are indefinite for the recitation of "vertebrate origin" as the claims do not indicate what organism. The claims are also indefinite for reciting "that would occur" because it implies that there are times that the condition may not occur (see also the recitation of "possibly" in claim 120).

Art Unit: 1653

Claim 120 is indefinite because the claim is not further limiting the independent claim (see also 126 and 131).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35

Art Unit: 1653

6. Claims 64-119 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Grantham et al. (Nucleic Acid Research, vol. 9, no. 1, pages r43-r74, 1981) taken with Seed et al. (U.S. Patent No. 5,795,737, August 18, 1998) and Capon et al. (U.S. Patent No. 4,965,199, October 23, 1990).

Grantham disclose the preferred codons used in different organisms and the frequencies of the codons in different genes. Grantham also disclose that codon choice is related to mRNA expressivity, that is the amount of protein made by a particular messenger (see r43). Grantham do not expressly teach a method of preparing a synthetic gene that encodes a protein.

Seed teaches synthetic genes and methods for preparing synthetic genes encoding proteins normally expressed by mammalian cells or other eukaryotic cells. The method includes identifying non-preferred codons in the natural gene encoding the protein and replacing one or more of the non-preferred and less-preferred codons with a preferred codon encoding the same amino acid as the replaced codon. Seed also teach that at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the codons in the natural gene are non-preferred codons (see column 2). As Seed teaches that one or more of the non-preferred or less-preferred codons are replaced with a preferred codon, a 33%, 94%, 98% or more codon replacement in a continuous stretch of the synthetic nucleic acid sequence is obtained as recited in the claims.

In addition, Seed teach that the synthetic gene encodes at least 50, 100, 150 or 500

Art Unit: 1653

codons or less-preferred codons. Replacement of a portion of these codons with preferred codons should yield genes capable of higher level expression in mammalian cell culture (see column 3).

Additionally, Seed teaches a vector and cell which includes a synthetic gene of the invention (see column 3). Seed also teaches a synthetic gene encoding the gp120 segment of HIV-1 (syngp120nm, see Figure 1A). According to Seed, in this synthetic gp120 gene nearly all of the native codons have been replaced with codons most frequently used in highly expressed human genes. Further, Seed teaches that this synthetic gene was assembled from chemically synthesized oligonucleotides of 150 to 200 bases in length (see column 8). Seed also teach that codon optimization is a fruitful strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes (see column 24). In-so-far-as Seed do not teach a non-transformed cell as recited in claims 82, 86, 90 and 102, Capon teaches a method of producing factor VIII in recombinant mammalian host cells. As Capon teaches that human factor VIII is produced in functional form in a particularly suitable host cell system. This system comprises baby hamster kidney cells which have been transfected with an expression vector comprising DNA encoding human factor VIII (see abstract and column 5)

In view of the foregoing, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Grantham identifies the preferred/common

codons and their frequency in highly expressed human genes.

Art Unit: 1653

construction of synthetic genes. Seed used HIVgp120, the rat cell surface antigen Thy-1 and green fluorescent protein from *Aequorea victoria* to illustrate that codon optimization is a beneficial strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes. Neither Grantham nor Seed teaches a non-transformed cell, however, Capon teaches the production of a Factor VIII in a recombinant mammalian host cell. Further, it is presumed that applicant meant to indicate that the Factor VIII polynucleotide was inserted into a non-transformed cell. One of ordinary skill in the art would be motivated to combine the above references to create a synthetic gene where one or more less-preferred or non-preferred codon is replaced by a common/preferred codon for codon optimization as taught by Seed, utilizing a host cell and expression vector as taught by Seed and Capon with a reasonably expectation of success because Grantham disclose that the amount of protein made by a particular messenger depends on the choices of codons used. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

7. Claims 64-119 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kim et al (Gene, vol. 199, pages 293-301, 1997) taken with Seed et al. (U.S. Patent No. 5,786,464, July 28, 1998) and Capon et al. (U.S. Patent No. 4,965,199, October 23, 1990)..

Kim disclose that the usage of selective codons in a given gene is positively correlated with the expression level of the gene. Seed et al. teach that the use of preferred codons in a gene increases the expression level of the gene. Capon et al. teach that the use of preferred codons in a gene increases the expression level of the gene.

Art Unit: 1653

codons frequently found in highly expressed human genes and the other with codons prevalent in yeast genes. The synthetic, mature EPO gene based on either human or yeast high frequency codons were assembled from eight 80-90 base oligonucleotides that were synthesized... (see pages 293-294). Kim does not disclose a synthetic nucleic acid *per se* which encodes Factor IX or Factor VIII.

Seed teaches synthetic genes and methods for preparing synthetic genes encoding proteins normally expressed by mammalian cells or other eukaryotic cells. The method includes identifying non-preferred codons in the natural gene encoding the protein and replacing one or more of the non-preferred and less-preferred codons with a preferred codon encoding the same amino acid as the replaced codon. Seed also teach that at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the codons in the natural gene are non-preferred codons (see column 1-2). As Seed teaches that one or more of the non-preferred or less-preferred codons are replaced with a preferred codon, a 33%, 94%, 98% or more codon replacement in a continuous stretch of the synthetic nucleic acid sequence is obtained as recited in the claims (see also claims 8 and 9 where Seed disclose that at least 50% or at least 90% of the non-preferred and less-preferred codons are replaced with preferred codons).

In addition, Seed teach that the synthetic gene encodes at least 50, 100, 150 or 500 contiguous amino acids of the protein (see columns 1-2). Seed further teaches that a large fragment of the synthetic gene is used to produce a protein. The fragment of the synthetic gene is used to produce a protein that is at least 50, 100, 150 or 500 amino acids long.

Art Unit: 1653

codons should yield genes capable of higher level expression in mammalian cell culture (see column 1-3).

Additionally, Seed teaches a vector and cell which includes a synthetic gene of the invention (see column 3). Seed also teaches a synthetic gene encoding the gp120 segment of HIV-1 (syngp120nm, see Figure 1A). According to Seed, in this synthetic gp120 gene nearly all of the native codons have been replaced with codons most frequently used in highly expressed human genes. Further, Seed teaches that this synthetic gene was assembled from chemically synthesized oligonucleotides of 150 to 200 bases in length (see column 8). Seed also teach that codon optimization is a fruitful strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes (see column 24). In-so-far-as Seed do not teach a non-transformed cell as recited in claims 82, 86, 90 and 102, Capon teaches a method of producing factor VIII in recombinant mammalian host cells. As Capon teaches that human factor VIII is produced in functional form in a particularly suitable host cell system. This system comprises baby hamster kidney cells which have been transfected with an expression vector comprising DNA encoding human factor VIII (see abstract and column 5).

In view of the foregoing, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Kim disclose that the level of gene expression of eukaryotic genes introduced into mammalian cells depends on gene copy number,

Art Unit: 1653

and the use of selective codons in a given organism and demonstrates this with the construction of a synthetic EPO gene (see pages 293-294). In addition, Seed also demonstrate codon optimization and its effect on mRNA expressivity with the construction of synthetic genes. Seed used HIVgp120, the rat cell surface antigen Thy-1 and green fluorescent protein from *Aequorea victoria* to illustrate that codon optimization is a beneficial strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes. Neither Kim nor Seed teaches a non-transformed cell, however, Capon teaches the production of a Factor VIII in a recombinant mammalian host cell. Further, it is presumed that applicant meant to indicate that the Factor VIII polynucleotide was inserted into a non-transformed cell. One of ordinary skill in the art would be motivated to combine the above references to create a synthetic gene where one or more less-preferred or non-preferred codon is replaced by a common/preferred codon for codon optimization as taught by Seed and Kim, utilizing a host cell and expression vector as taught by Capon, with a reasonably expectation of success because both references disclose a positive effect on expression with preferred choices of codons. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

8. Claims 120-135 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Grantham et al. (Nucleic Acid Research, vol. 9, no. 1, pages r43-r74, 1981) taken with Seed et al

Art Unit: 1653

The teachings of Grantham and Seed as applied to claims 64-119 are above. Neither Grantham or Seed expressly teach a primary and secondary cell of vertebrate origin having an exogenous synthetic nucleic acid sequence. However, Kuo teach that the Factor VIIIc genomic DNA sequences containing both exons and introns may be inserted into an expression vector appropriate for transcription and translation in mammalian cells to provide for both substantial quantities of properly spliced messenger RNA suitable for cDNA cloning and production of Factor VIIIc subunits or fragments. In addition, Kuo teach that the DNA sequences isolated from the genome can be used for hybridizing to natural messenger RNA(mRNA) encoding for Factor VIIIc. The mRNA may then be used to prepare cDNA encoding Factor VIIIc. The cDNA sequences may be employed for expression by insertion into an appropriate expression vector having the necessary regulatory signals for transcription and translation. Kuo also teach that the Factor VIIIc gene expression vector (an expression vector carrying one or more genes encoding for all or a portion of Factor VIIIc, precursor, subunits or fragments thereof) may be introduced into a compatible host and the host grown for expression of Factor VIIIc (see column 3).

In addition, Kuo teach that various vectors may be employed for providing extrachromosomal elements, depending upon the particular host, the manner of expression, whether secretion is desired or the like. Kuo also teach that vectors are presently available which provide for the transcriptional and translational regulatory signals recognized either by mammalian

Art Unit: 1653

transcriptional and translational signals recognized by the host. The transcriptional signals will include the promoter and terminator as well as auxiliary signals such as one or more enhancers. Additionally, regulation of transcription may be provided, by including operators, activators, genes providing for repression or the like. Other sequences involved with transcription include capping, polyadenylation, etc. Furthermore, for translation, depending upon the host, there may be a ribosomal binding site, an initiation codon, stop codons or the like (see columns 3-9).

In view of the foregoing it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Grantham identifies the preferred/common codons and their frequency of use in different genes. Further, Grantham indicates that there is an association between codon choice and mRNA expressivity and Seed demonstrates this with the construction of synthetic genes. Seed used HIVgp120, the rat cell surface antigen Thy-1 and green fluorescent protein from *Aequorea victoria* to illustrate that codon optimization is a beneficial strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes. Although Grantham and Seed do not expressly teach a primary or secondary cell of vertebrate origin having an exogenous synthetic nucleic acid sequence, Kuo teaches an expression system in mammalian cells where the vector carries one or more genes encoding for all or a portion of Factor VIIIc, precursor, subunits or fragments (see column 3). One of ordinary skill in the art would be motivated to combine the above references because Seed teaches that expression

Art Unit: 1653

the endogenous codons with codons over represented in highly expressed prokaryotic genes. Seed also teach that rare codons cause pausing of the ribosome, which leads to a failure to complete the nascent polypeptide chain and an uncoupling of transcription and translation. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

Conclusion

9. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Hope A. Robinson whose telephone number is (703)308-6231. The Examiner can normally be reached on Monday - Friday from 9:00 A.M. to 5:30 P.M. (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor Christopher S.F. Low, can be reached at (703)308-2932.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703)308-0196.

Papers related to this application may be submitted by facsimile transmission. The official

Application/Control Number: 09/407,605

Page 16

Art Unit: 1653

The faxing of such papers must conform with the notice published in the Official Gazette, 1096
OG (November 15, 1989).

Hope A. Robinson, MS *HR*

Patent Examiner

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